UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff, v. DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC., Defendants.	Civil Action No. 19-18686-MAS-TJB *Electronically Filed*

DECLARATION OF DR. JERRY ATWOOD
IN SUPPORT OF PLAINTIFF'S OPENING CLAIM CONSTRUCTION BRIEF

I, Jerry L. Atwood, hereby declare the following:

I have been asked by Bristol Myers-Squibb Company ("BMS") to prepare an expert declaration addressing the meaning of one (1) of the two (2) disputed terms—"an x-ray powder diffraction pattern . . . comprising four or more 2θ values selected from the group consisting of"—in the asserted claims of BMS' U.S. Patent Nos. 7,491,725 ("the '725 patent"), 8,242,270 ("the '270 patent"), and 8,680,103 ("the '103 patent") (attached herein as Exs. A-C). In rendering my opinions, I have reviewed, *inter alia*, the patents and their prosecution histories, Dr. Reddy's proposed claim construction, and the documents cited in the Joint Claim Construction statement.

I. QUALIFICATIONS[1]

1. From 1994-2016, I was employed as Professor and Chairman of the Department of Chemistry at the University of Missouri-Columbia. From 2000-2019, I held the position of Curators' Distinguished Professor of Chemistry at the University of Missouri-Columbia. Since

[1] Attached herein as Exhibit D is my curriculum vitae.

2020, I am Curators' Distinguished Professor of Chemistry Emeritus at the University of Missouri-Columbia. From 1968 to 1994, I was employed by the University of Alabama, where I successively held the titles of Assistant Professor, Associate Professor, and University Research Professor. I earned my Ph.D. degree in Chemistry from the University of Illinois in 1968.

2. From 1985 to 1998, I was Editor of the *Journal of Chemical Crystallography*. From 1992 until 2000, I was Editor of *Supramolecular Chemistry*. From 1985 to 1993, I was Regional Editor for the *Journal of Coordination Chemistry*. I was Co-Editor-in-Chief of the *New Journal of Chemistry* from 2005-2010. I am a Co-Editor of the *Inclusion Compounds* book series (five volumes), *Comprehensive Supramolecular Chemistry* (ten volumes), and the *Encyclopedia of Supramolecular Chemistry* (2 volumes). I am co-author of the text *Supramolecular Chemistry*, currently in its third edition. I currently serve on the editorial boards of *Crystal Growth & Design,* the *Journal of Coordination Chemistry,* and *Supramolecular Chemistry*. From 1999-present, I am Advising Editor for the *Journal of Chemical Crystallography*.

3. I currently run an active research laboratory of one postdoctoral fellow and four graduate students. I have published more than 750 articles in refereed journals, most of which focus on the fields of crystal growth, crystal engineering, polymorphism, organic chemistry and polymer chemistry.

II. BACKGROUND INFORMATION

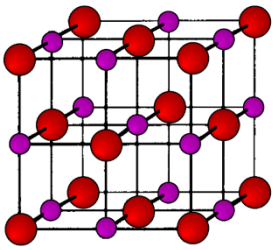
4. The following tutorial is provided as general scientific information to both assist the Court and explain the meaning of the disputed claim term. There may be exceptions or caveats to the scientific statements made here, but I provide the general concepts only to be concise.

a. Polymorphs

5. A compound is a substance made by joining together atoms of different chemical elements (such as carbon, oxygen or hydrogen for example) in a specific ratio and connectivity, resulting in a specific chemical structure. The different atoms are connected by chemical bonds. A compound has properties that are different from those possessed by the elements that comprise it. The smallest fundamental unit of a compound that retains the compound's properties is a molecule.

6. Some compounds can adopt crystalline forms. A crystal consists of repeating units made up of a regularly ordered arrangement of molecules or ions in three dimensional space. These units are referred to as unit cells. There are seven different unit cell shapes: triclinic, monoclinic, orthorhombic, tetragonal, hexagonal, trigonal and cubic.

7. An example of a crystalline compound is table salt, NaCl. Table salt is a compound comprised of sodium (Na^+) ions and chloride (Cl^-) ions. A regularly ordered arrangement of these ions in three dimensional space results in a cubic lattice.



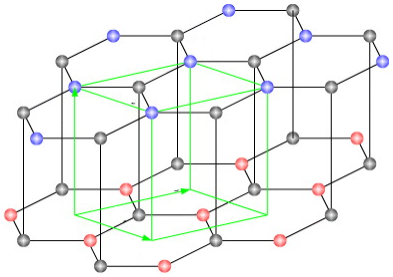
Crystalline Structure of salt (NaCl)

Sodium ions are shown as small spheres and chloride ions are shown as large spheres.

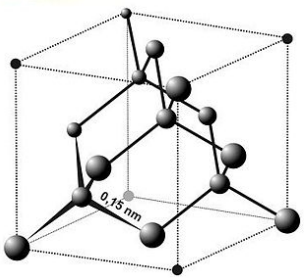
8. It is possible for a compound to crystallize into more than one distinct crystalline form. These distinct crystalline forms are referred to as polymorphs. Polymorphs of a particular compound have identical chemical structures, but the arrangement of the molecules of the

compound in three dimensional space, *i.e.*, the crystal structure, is different, resulting in different physical properties.

9. Examples of polymorphs are graphite and diamond. Both are made up of carbon atoms, but the arrangement of the atoms in three-dimensional space is different, resulting in very different properties. Graphite is opaque and has a dull metallic sheen, while diamonds are transparent and brilliant. Another difference is that graphite is one of the softest natural substances whereas diamond is the hardest.



Graphite - a staggered arrangement of stacked hexagonal layers



Diamond - tetrahedrally bonded carbon atoms

10. Once obtained, polymorphs can be characterized by a variety of different techniques. As discussed in more detail below, one of these techniques is X-ray powder diffraction ("XRPD"), which provides information about the spacing between the planes of atoms in a crystal lattice.

11. Different polymorphs of a given molecule can display significantly different properties, such as different stabilities (e.g., how, if at all, a drug's properties vary over time), different dissolution profiles (e.g., the amount of drug product that dissolves over a given period of time), and different bioavailability (e.g., the amount of drug product available in the human body to have an active effect). These different properties can be of great significance in the

pharmaceutical industry. For example, these differences can affect the manufacturability, performance, and quality of the drug product.

12. An understanding of the different polymorphs of a particular pharmaceutical is important because information about how the polymorphs convert from one polymorphic form to another, and about their advantages over each other, may affect the properties of the final drug product. Thus, for a manufacturer to be able to control its drug manufacturing methods and have confidence in the end product of those methods, the manufacturer should have an understanding of whether polymorphs exist and the characteristics of the polymorphs if they do exist.

b. Solvates, Hydrates, and Anhydrates

13. Some substances can trap solvent while undergoing crystallization in a definite ratio as an integral part of the crystal structure, resulting in a crystalline solvate. When the solvent is water, the compound is referred to as a hydrate. If a single water molecule is trapped for every single molecule of a substance, it is known as a monohydrate. When no solvents or water molecules are trapped in the crystal lattice, it is referred to as an anhydrate (or "neat" form). These terms refer to the smallest repeating unit of the pattern making up the crystal. In a sample, there may be crystals that are monohydrate and crystals that are anhydrate, for example.

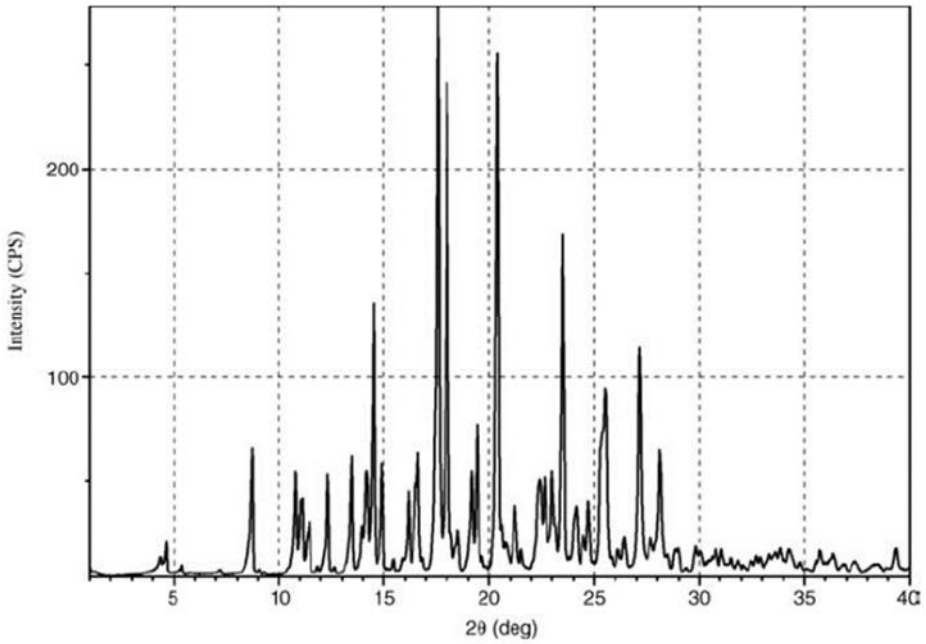
14. For certain compounds, the same crystal structure can have different kinds of solvent molecule trapped within it. Such structures are referred to as isostructural solvates, or channel solvates. In other words, the molecules in solvates that are isostructural have approximately the same positions and orientations in the crystal structure, even if they have different solvents in their structure.

c. X-ray Powder Diffraction

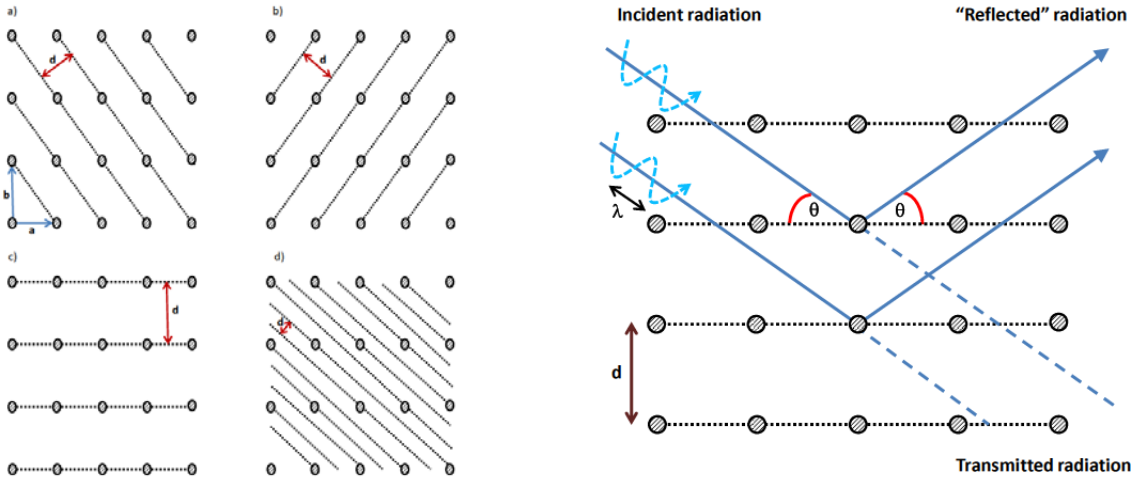
15. A crystalline solid is one in which the molecules or atoms are uniformly arranged in a "crystal lattice." This uniform arrangement gives rise to a unit cell, which is the simplest repeating three-dimensional portion of the crystal structure. The crystal lattice is therefore built up by stacking the unit cell in three dimensions. The size, shape, and contents of each unit cell within a crystal are identical. For example, diamond is a crystalline form of carbon and consists of an ordered arrangement of carbon atoms.

16. X-ray powder diffraction ("XRPD") data can be used to distinguish different polymorphs or solvate forms of a crystalline compound. X-ray powder diffraction is a method of characterizing solid substances in which a sample is bombarded with X-rays, those X-rays bounce off the crystals at different angles (*e.g.*, the X-rays "diffract"), and those diffracted X-rays are then recorded by a detector. A crystalline compound diffracts X-rays according to the arrangement of molecules in the crystal structure. Because crystalline solids are built in an ordered way, the same motifs repeat throughout the crystal in the three dimensions, which creates the lattice. These lattices exhibit "planes" in 3-D space. Different planes can occur in a particular crystal structure.

17. An X-ray powder diffraction pattern plots the intensity of an X-ray beam diffracted by the crystal lattice versus the angle of diffraction of the X-rays, usually represented with a measurement value of 2θ. Below is an example of an X-ray diffraction pattern where the X-axis plots the 2θ values and the Y-axis plots the intensity of the diffracted X-ray beam:



18. When preparing a sample for X-ray powder diffraction, the material of interest is generally ground into a fine crystalline powder. When X-rays of a particular wavelength are directed at the powder, the diffracted x-rays are detected and, if plotted, an observable pattern is produced. This is because the X-rays are electromagnetic waves that interact with the planes of the lattice in a distinct manner. For purposes of illustration, the three-dimensional planes can be represented in two-dimensional space, wherein the lines represent planes. The wavelength of the X-rays that are used in such an experiment is of a length that is similar to the distance between the planes within the crystal, represented by the letter "d." The X-ray beam reflects off the crystallographic plane, and the angle of reflection is the same as the angle of incidence.



A lattice plane is a plane which intersects atoms of a unit cell across the whole three-dimensional lattice. The perpendicular separation between each plane is called the d-spacing.

19. The result of an XRPD experiment is a pattern that can be used to identify a particular crystal structure or polymorph. This is possible because all possible lattice planes for the diffraction of X-rays are present in the crystalline powder sample. For every d-spacing between lattice planes, a device, called a diffractometer, plots the intensity of the diffracted X-rays versus the angle of incidence, usually represented as 2θ. The intensity of the diffracted X-rays relates to the arrangement of the molecules in the lattice, and is often provided as relative intensity, in which the various peaks are divided by the intensity of the maximum peak. Because different polymorphs have different lattice structures, and therefore different lattice "planes," different polymorphs have a different set of 2θ values compared to related polymorphs. This is what allows the X-ray diffraction pattern to act as an identifier for a given crystal form of a particular compound. It is possible for different crystals or polymorphs to have one or more peaks in common, because they might have different planes that have a similar d-spacing. However, it does not mean that the polymorphs share these particular planes. Therefore, the selection of multiple peaks from an XRPD pattern can be used to identify and distinguish the

crystalline form of a compound from other crystalline forms of the same compound (polymorphs).

20. In addition, the relative peak intensities can vary depending on the orientation of the sample. Severe preferential crystalline particle orientation can be induced by the particle size, leading to skewed X-ray powder diffraction data with regard to the intensities of the peaks. Preferred orientation is especially a problem with polymorphs that have needle-like or plate-like crystals. (*See* Ex. E, West, at 139.) Even if the preferred orientation of the sample is accounted for, the relative intensities can vary. Moreover, this potential variance is on a peak-by-peak basis.

III. CLAIM CONSTRUCTION ANALYSIS

21. The ’725, ’270 and ’103 patents relate to crystalline forms of dasatinib. The art disclosed in these patents relates to solid-state chemistry and the design of a solid or crystalline form of an active pharmaceutical ingredient (“API”) that is stable yet readily bioavailable. The person of ordinary skill in the art (“POSA”) would be a medicinal or synthetic chemist with an advanced degree in solid-state chemistry with considerable study in pharmacology and crystal engineering. The person of ordinary skill would either work with a person with an advanced degree in molecular biology with education or experience in the field of cellular signal transduction or would have such training himself. I consider myself one example of a POSA. That said, my opinions would not change using DRL’s definition of a POSA.

A. “an x-ray powder diffraction pattern . . . comprising four or more 2θ values selected from the group consisting of . . . .”

22. This phrase appears in claim 3 of the ’725 patent, claim 3 of the ’103 patent, and claims 7 and 9 of the ’270 patent. I understand the parties have offered the following constructions for the term “an x-ray powder diffraction pattern . . . comprising four or more 2θ values selected from the group consisting of . . . .”:

BMS CONSTRUCTION	DRL CONSTRUCTION
Plain meaning as understood by a person of ordinary skill in the art, i.e., "having at least four 2θ values selected from the group consisting of."	"an x-ray powder diffraction pattern comprising four or more of the claimed 2θ values and having no additional 2θ values not identified in the claim."

23. The phrase at issue is followed in each claim by a list of specific 2θ values. Claim 3 of the '725 patent recites the following eight (8) 2θ values: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2. Claim 3 of the '103 patent likewise lists the following eight (8) 2θ values: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2.

24. The specification of the '725 and '103 patents lists each of the values recited in claim 3 of the '725 patent, and claim 3 of the '103 patent in Example 8, which is directed to a "crystalline monohydrate" of dasatinib. '725 Patent, 43:48-49; '103 Patent, 45:16-17. Example 8 indicates that "[o]ne of ordinary skill in the art will appreciate that the monohydrate of the compound of formula (IV) may be represented by the XRPD as shown in Fig. 1…" '725 patent, 44:23-25. The XRPD pattern in Figure 1 shows at least thirty-one (31) 2θ values. '725 Patent, 25:6-9; '103 Patent, 24:62-6; Fig. 1. Figure 1 is an exemplified embodiment of the monohydrate of the compound of formula (IV) claimed in claim 3 of the '725 patent, and claim 3 of the '103 patent.

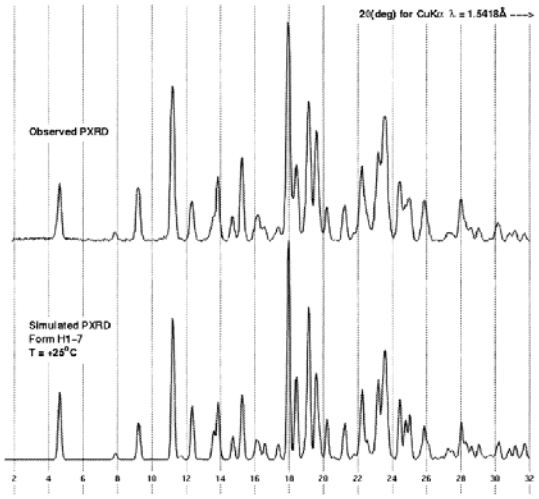


Figure 1

25. Claim 7 of the '270 patent lists the following nine (9) 2θ values: 6.8±0.2, 11.1±0.2, 12.3±0.2, 13.2±0.2, 13.7±0.2, 16.7±0.2, 21.0±0.2, 24.3±0.2, and 24.8±0.2. The specification recites these same values in Example 11, which describes a "crystalline" dasatinib "[n]eat form N-6." '270 Patent, 48:61-64; 49:34-36. Example 11 teaches that "[o]ne of ordinary skill in the art will appreciate that the crystalline form of the compound of formula (IV) may be represented by the XRPD as shown in FIG. 5." '270 patent, 49:30-32. Figure 5 shows at least fifteen (15) 2θ values. Fig. 5. Figure 5 is an exemplified embodiment of the compound of formula (IV) claimed in claim 7 of the '270 patent.

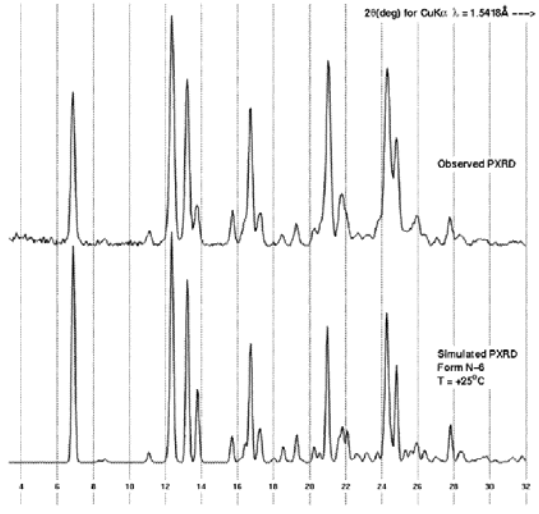


Figure 5

26. Claim 9 of the '270 patent lists the following eight (8) 2θ values: 8.0±0.2, 9.7±0.2, 11.2±0.2, 13.3±0.2, 17.5±0.2, 18.9±0.2, 21.0±0.2, and 22.0±0.2. The specification recites these same values in Example 12, which describes a "crystalline" dasatinib "neat form T1H1-7." '270 Patent, 49:43-46, 65-67. Example 12 teaches that "[o]ne of ordinary skill in the art will appreciate that the neat crystalline form (T1H1-7) of the compound of formula (IV) may be represented by the XRPD as shown in FIG. 6." '270 patent, 49:61-63. Figure 6 shows at least twenty (20) 2θ values. Fig. 6. Figure 6 is an exemplified embodiment of the compound of formula (IV) claimed in claim 9 of the '270 patent.

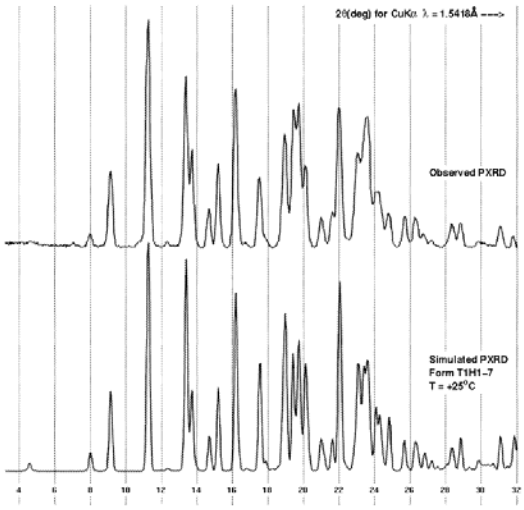


Figure 6

27. BMS' construction is consistent with how a POSA would understand the claims. One of ordinary skill in the art would understand the phrase "an x-ray powder diffraction pattern . . . comprising four or more 2θ values selected from the group consisting of . . . ." to mean that which is characterized by an x-ray powder diffraction pattern having at least four of the recited 2θ values. One of ordinary skill in the art would understand that a standard XRPD pattern of the crystalline monohydrate of the compound of formula (IV), or the crystalline compound of formula (IV) as recited in the claims will have other 2θ values in addition to those recited in the

claims. A POSA would understand that the 2θ values recited represent that which may be used to identify the claimed forms in a given XRPD pattern, even if other unclaimed 2θ values also appear in the XRPD pattern.

28. Under DRL's construction, the exemplified embodiment of the claims would not be covered by the claims. For instance, Figure 1 is an XRPD pattern having at least 31 2θ values. Under DRL's construction, Figure 1 has more than the recited eight 2θ values, and therefore would fall outside of claim 3 of the '725 patent and claim 3 of the '103 patent. On the other hand, under BMS' construction, Figure 1 would be covered by claim 3 of the '725 patent, and claim 3 of the '103 patent, in line with the teachings of the specification, which describes Figure 1 as a preferred embodiment of the claims. *See, e.g.*, '725 patent at 44:23-25. That is, the crystalline monohydrate of the compound of formula (IV) in Figure 1, when characterized by standard XRPD values, produces the 2θ values recited in the claims. The same can be said regarding claims 7 and 9 of the '270 patent.

29. A POSA's experience furthermore supports BMS' understanding of the claims. As a general matter, an XRPD pattern of a crystalline compound will contain more than nine (9) 2θ values. This is confirmed by the examples of the patent. Figure 1 includes a calculated pattern that shows the expected XRPD pattern independent of experimental factors. '725 Patent, 4:62-65, 44:23-26, 45:12-13. The same goes for Figures 5 and 6 of the '270 patent. '270 patent, 5:25-32.

30. Based on the exemplified crystalline forms of formula (IV), and their own experience, a POSA would expect that an XRPD pattern of all monohydrate or anhydrate forms of dasatinib may have more than the eight or nine 2θ values recited in the claims. Under DRL's construction, no monohydrate or anhydrate would be covered by the claims. Under BMS'

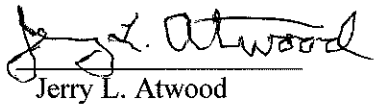
construction, variations of the Figure 1 monohydrate, or Figure 5 or 6 anhydrate, could be covered by the claims.

31. A POSA would understand the claims as construed by BMS, and not by DRL.

32. I may supplement my opinion as necessary to respond to the arguments raised by DRL or its retained experts, including as to the other disputed term at issue, "crystalline compound of formula (IV)," from claims 7-9 of the '270 patent.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Date: July 29, 2020



Jerry L. Atwood